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10/701,007	11/04/2003	Charles Allerson	ISIS-5325	5641

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WOODCOCK WASHBURN LLP
CIRA CENTRE, 12TH FLOOR
2929 ARCH STREET
PHILADELPHIA, PA 19104-2891

EXAMINER	
ZARA, JANE J	
ART UNIT	**PAPER NUMBER**
1635	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	03/26/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	10/701,007	ALLERSON ET AL.	
	Examiner	Art Unit	
	Jane Zara	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *23 February 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *4-7,34,37,38,46,49-51,53-63,65,72,74-78,94-96,100 and 104* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *4-7, 34, 37, 38, 46, 49-51, 53-63, 65, 72, 74-78, 94-96, 100 and 104* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

This Office action is in response to the communication filed 2-23-07.

Claims 4-7, 34, 37, 38, 46, 49-51, 53-63, 65, 72, 74-78, 94-96, 100 and 104 are pending in the instant application.

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 2-23-07 has been entered.

Response to Arguments and Amendments

Withdrawn Rejections

Any rejections not repeated in this Office action are hereby withdrawn.

Applicant's arguments with respect to claims 4-7, 34, 37, 38, 46, 49-51, 53-63, 65, 72, 74-78, 94-96, 100 and 104 have been considered but are moot in view of the new ground(s) of rejection set forth below.

New Rejections

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claim 100 is rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the in vitro targeting and inhibition of a target gene of known sequence using modified siRNA, does not reasonably provide enablement for methods of inhibition any target gene in vivo. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

The claim is drawn to methods of inhibiting gene expression in cells and tissues in an animal, comprising administration of any siRNA compound.

The following factors have been considered in determining that the specification does not enable the skilled artisan to make and/or use the invention over the scope claimed.

The state of the prior art and the predictability or unpredictability of the art. The following references are cited herein to illustrate the state of the art of nucleic acid treatment in organisms. Branch teaches that the in vivo (whole organism) application of nucleic acids (such as antisense) is a highly unpredictable endeavor due to target

accessibility and delivery issues. Cell culture examples are generally not predictive of in vivo inhibition of target genes (A. Branch, Trends in Biochem. Sci. 23: 45-50).

Likewise, Peracchi cautions investigators in the field of gene therapy about the problems of achieving in vivo efficacy using oligonucleotide based approaches Peracchi cites stability and delivery obstacles that need to be overcome in achieving desired in vivo efficacy: "A crucial limit of ribozymes in particular, and of oligonucleotide-based drugs in general, lies in their intrinsically low ability to cross biological membranes, and therefore to enter the cells where they are supposed to operate...cellular uptake following systemic administration appears to require more sophisticated formulations... the establishment of delivery systems that mediate efficient cellular uptake and sustained release of the ribozyme remains one of the major hurdles in the field." (A. Peracchi et al, Rev. Med. Virol., 14: 47-64, especially at 51).

Agrawal et al also speak to the unpredictable nature of the nucleic acid based therapy field thus: "It is therefore appropriate to study each ... oligonucleotide in its own context, and relevant cell line, without generalizing the results for every oligonucleotide (S. Agrawal et al., Molecular Med. Today, 6: 72-81 at 80). Cellular uptake of oligonucleotides by appropriate target cells is another rate limiting step that has yet to be overcome in achieving predictable clinical efficacy using antisense." Both Chirila et al and Agrawal et al point to the current limitations which exist in our understanding of the cellular uptake of ... oligonucleotides in vitro and in vivo (see Agrawal et al especially at pages 79-80; *see* Chirila et al., Biomaterials, 23: 321-342 in its entirety,

especially at 326-327 for a general review of the important and inordinately difficult challenges of the delivery of therapeutic oligonucleotides to target cells).

See also the discussion by Opalinska et al of unpredictability of nucleic acid therapy, including the use of siRNA and antisense in vivo (Opalinska et al, Nature Rev., 1: 503-514, at 503 and 511). "Although conceptually elegant, the prospect of using nucleic-acid molecules for treating human malignancies and other diseases remains tantalizing, but uncertain... The main cause of this uncertainty is the apparent randomness with which these materials modulate the expression of their intended targets. It is a widely held view that molecule delivery, and selection of which messenger RNA sequence to physically target, are core stumbling blocks that hold up progress in the field. ...it is widely appreciated that the ability of nucleic-acid molecules to modify gene expression in vivo is quite variable, and therefore wanting in terms of reliability." [references omitted].

The amount of direction or guidance presented in the specification AND the presence or absence of working examples. Applicants have not provided guidance in the specification toward a method of inhibiting gene expression in vivo using any siRNA.

The ability to inhibit target gene expression in vitro is not representative or correlative of the ability to inhibit gene expression in vivo. In addition, one skilled in the art would not accept on its face the examples given in the specification of in vitro inhibition as being correlative or representative of the ability to inhibit any target gene in a subject in vivo in view of the lack of guidance in the specification and known

unpredictability associated with the ability to predict the efficacy of interfering RNA in inhibiting the expression of target gene in an organism.

The breadth of the claims and the quantity of experimentation required. The breadth of the claims is very broad. The claims are drawn to compositions and methods of any target gene in vivo using any RNAi. The quantity of experimentation required to practice the invention as claimed would require the *de novo* determination of accessible target sites, modes of delivery and formulations to target appropriate cells and /or tissues harboring the target gene to be inhibited, whereby its expression is inhibited in vivo following the administration, by any means, of any RNAi of any size, comprising the instantly claimed modifications.

Since the specification fails to provide any particular guidance for the successful targeting and inhibition of expression of target genes in vivo comprising administration of any RNAi encompassed by the broad genus claimed, and since determination of these factors is highly unpredictable, it would require undue experimentation to practice the invention over the scope claimed.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains.

Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 4-7, 34, 37, 38, 46, 49-51, 53-63, 65, 72, 74-78, 94-96, 100 and 104 are rejected under 35 U.S.C. 103(a) as being unpatentable over Elbashir et al (EMBO J., vol. 20, No. 23, pages 6877-6888, 2001), Fosnaugh et al (US 2003/0143732) and Morrissey et al (US 2003/0206887) in view of the combined teachings of Arnold et al (USPN 6,262,036), Damha et al (US 2005/0142535) and McKay et al (USPN 6,133,246) insofar as the claims are drawn to compositions and methods of inhibiting gene expression in a cell in vitro comprising administration of compositions comprising chemically synthesized siRNA oligonucleotides comprising various motifs, the motifs in turn comprising nucleosides different in their 2'-substituent groups, and optionally include H, OH as first and second types of nucleosides, or alternatively comprising motifs of 2'-substituent groups which are optionally fluoro or methoxyalkyl groups of various alkyl chain lengths, and which oligonucleotides optionally further comprise, in addition to different motifs of differing 2'-substituent containing motifs, internucleotide

linkage modifications comprising phosphorothioate internucleotide linkages, and which oligonucleotides optionally further comprise 3'-and/or 5'-terminal caps, optionally including inverted deoxy abasic moieties, and which comprise alternating 2'-β-D-deoxynucleosides with 2'-modified nucleosides.

Elbashir et al (EMBO J., vol. 20, No. 23, pages 6877-6888, 2001) teach methods of target gene inhibition in embryo lysates comprising siRNA molecules comprising 2'-deoxy and 2'-O-methyl substitutions. Elbashir et al teach a correlation between the placement of 2'-substitutions on the oligonucleotides and the retention of siRNA activity (see esp. the abstract on p. 6877, fig. 8 and text on p. 6885).

Fosnaugh et al (US 2003/0143732) teach various motifs and configurations of 2'-modifications, including fluoro or methoxyalkyl groups of various alkyl chain lengths, and which oligonucleotides optionally further comprise, in addition to different motifs of differing 2'-substituent containing motifs, internucleotide linkage modifications comprising phosphorothioate internucleotide linkages, and which oligonucleotides optionally further comprise 3'-and/or 5'-terminal caps and optionally including inverted deoxy abasic moieties on the termini, and the effect of arrangements of these different modifications on siRNA ability to bind to and inhibit target gene expression in the presence of RISC. Fosnaugh et al also teach compositions comprising modified and unmodified siRNAs and RISC for target gene inhibition see p. 1, 3-4, 6-9, p. 16 and figures 4 and 5, claim 30).

Morrissey et al (US 2003/0206887) teach various ways of designing and optimizing 2'-O-modifications on siRNA, including fluoro or methoxyalkyl groups of

various alkyl chain lengths, and abasic, inverted abasic termini and 5' and 3' capped termini, and the effect of various motifs or arrangements of these 2'substitutuents and modified phosphorothioate internucleotide linkages on target gene inhibition by siRNA in compositions further comprising RISC (see fig. 4 and 5, page 1, right col., p. 6, right col., p. 9, p. 20-21, claims 20-25).

The primary references of Elbashir et al, Fosnaugh et al and Morrissey et al do not teach alternating 2'-β-D-deoxynucleosides with 2'-modified nucleosides.

Arnold et al (USPN 6,262,036) teach antisense oligonucleotides comprising alternating 2'-β-D-deoxynucleosides with 2'-modified nucleosides, and the introduction of these modifications for enhancing target binding stability (see esp. example 34, col. 48-50).

Damha et al (US 2005/0142535) teach alternating 2'-β-D-deoxynucleosides with 2'-modified nucleosides in antisense oligonucleotides for enhancing target binding by antisense molecules for the binding and inhibition of target gene expression.

McKay et al (USPN 6,133,246) teach numerous motifs and combinations of modified residues within antisense oligonucleotides, including the incorporation of 2'-modified sugars which include 2'-fluoro, 2'-bromo, 2'-O-alkyl groups, modified nucleobases, modified internucleotide linkages, 2'-β-D-deoxynucleosides and combinations thereof, as well as the optimization of modifications for maximizing target binding, cellular uptake and oligonucleotide stability (see esp. col. 7-12; Tables 4-26, esp. Tables 11 and 12, and Table 26).

It would have been obvious to incorporate various motifs and configurations of 2'-modifications, including fluoro or methoxyalkyl groups of various alkyl chain lengths, and which oligonucleotides optionally further comprise, in addition to different motifs of differing 2'-substituent containing motifs, internucleotide linkage modifications comprising phosphorothioate internucleotide linkages, and which oligonucleotides optionally further comprise 3'-and/or 5'-terminal caps and optionally including inverted deoxy abasic moieties on the termini into siRNA molecules for enhancing their target binding and stability, yet minimizing inactivation of the siRNA ability to inhibit target gene expression because Elbashir et al, Fosnaugh et al and Morrissey et al all teach the designing and testing of various arrangements of modified siRNA for their ability to inhibit target gene expression. One of ordinary skill in the art would have incorporated alternating 2'-β-D-deoxynucleosides with 2'-modified nucleosides into RNAi molecules because it was well known at the time of the invention that such alternating modifications enhanced target binding stability of the antisense oligonucleotides for their target regions, as taught previously by Arnold et al and Damha et al. One of ordinary skill would have expected that the incorporation of these modifications are optimized using routine experimentation because Damha, McKay and Arnold all teach optimization experiments where antisense oligonucleotides comprising an array of different combinations of these well known modifications are tested for their ability to target and bind target genes and inhibit their expression, the ability to incorporate the modifications claimed were well known in the art, and testing different motifs was very routine at the time the instant invention was made. One of ordinary skill in the art would

have been motivated to combine the teachings of Elbashir et al, Fosnaugh et al and Morrissey et al, as applied to modifying and testing the activity of siRNA, with the teachings by McKay, Damha and Arnold regarding the incorporation of modifications into inhibitory oligonucleotides, for enhancing their ability to bind a target gene and for their ability to enhance oligonucleotide stability, and design the motifs instantly claimed, including alternating 2'-β-D-deoxynucleosides with 2'-modified nucleosides.

One of ordinary skill in the art would have expected that the siRNA molecules, modified with the various and appropriate configurations would provide target gene cleavage in the presence of an appropriate target gene sequence and in the presence of appropriately modified siRNA. One of ordinary skill in the art would have produced various motifs as a matter of design choice and optimizing 2'-O modified motifs within the siRNA while maintaining its siRNA activity would have been a matter of design choice after testing various modifications and their combinations in a manner previously done by many in the art for antisense, such as McKay and Arnold. One of ordinary skill in the art would have designed and tested such modification motifs because it was well known in the art at the time of the instant invention that incorporation of 2'-O-methoxy alky or 2'-deoxy, or 2'-fluoro modifications at appropriate positions within the siRNA allows for enhanced oligonucleotide stability, target binding and the trigger of target gene degradation by RISC. One of ordinary skill in the art would also have been motivated to incorporate 5', and/or 3' caps, including abasic and inverted abasic nucleotide or other terminal well known caps because these modifications were well known in the art to protect oligonucleotides from degradation, as taught previously by

Morrissey. Therefore the instant invention as a whole would have been prima facie obvious to one of ordinary skill at the time it was made.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 4-7, 34, 37, 38, 46, 49-51, 53-63, 65, 72, 74-78, 94-96, 100 and 104 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 36, 40, 44, 46-49, 52-64, 74-80, 93, 98-100 and 104 of copending Application No. 10/860,265. Although the conflicting claims are not identical, they are not patentably distinct from each other because both applications are drawn to in vitro methods and compositions comprising siRNA comprising various combinations of modifications, which modifications comprise 2'-substituted sugars,

modified internucleotide linkages, inverted deoxy abasic moieties, 5' and 3' terminal caps and optionally further comprising conjugated groups attached at the oligonucleotide termini.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Claims 4-7, 34, 37, 38, 46, 49-51, 53-63, 65, 72, 74-78, 94-96 and 104 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-24 of copending Application No. 11/054,848. Although the conflicting claims are not identical, they are not patentably distinct from each other because both applications are drawn to compositions comprising siRNA comprising various combinations of modifications, which modifications comprise 2'-substituted sugars, modified internucleotide linkages, inverted deoxy abasic moieties, and 5' and 3' terminal caps.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Conclusion

Certain papers related to this application may be submitted to Art Unit 1635 by facsimile transmission. The faxing of such papers must conform with the notices published in the Official Gazette, 1156 OG 61 (November 16, 1993) and 1157 OG 94 (December 28, 1993) (see 37 C.F.R. ' 1.6(d)). The official fax telephone number for the

Group is 571-273-8300. NOTE: If Applicant does submit a paper by fax, the original signed copy should be retained by applicant or applicant's representative. NO DUPLICATE CO PIES SHOULD BE SUBMITTED so as to avoid the processing of duplicate papers in the Office.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jane Zara whose telephone number is (571) 272-0765. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James Douglas Schultz, can be reached on (571) 272-0763. Any inquiry regarding this application should be directed to the patent analyst, Katrina Turner, whose telephone number is (571) 272-0564. Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Jane Zara
3-16-07

TC1600

JANE ZARA, PH.D.
PRIMARY EXAMINER